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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/661,415	09/12/2003	Andrew Vaillant	029849-0205	6654

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EXAMINER	
HURT, SHARON L	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 04/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/661,415	VAILLANT ET AL.	
	Examiner	Art Unit	
	Sharon Hurt	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *10 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *3-13 and 33-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,14-32 and 38* is/are rejected.

7)☒ Claim(s) *14-33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *Nov. 26, 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group II, claims 1-2, 14-32 and 38, in the reply filed on April 10, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election **without traverse** (MPEP § 818.03(a)).

Claims 3-13 and 33-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on April 10, 2006.

Claims 1-2, 14-32 and 38 are examined in the instant application.

Claim Objections

Claims 14-32 are objected to because of the following informalities: Claims are drawn to a non-elected invention, a pharmaceutical composition or kit. Claims 14-33 are objected to because they are dependent on non-elected or withdrawn claims, 3 and 12. Appropriate correction is requested.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 14-32 and 38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method for the prevention or treatment of RSV and parainfluenza virus comprising administration of an oligonucleotide at least 10 or 40 nucleotides in length with anti-viral activity occurring principally by a non-sequence complementary mode of action. The specification and claims do not adequately describe the distinguishing features or attributes concisely shared by the members of the genus comprising oligonucleotides with non-sequence complementary mode of action and comprising random sequences, whereby prevention and treatment of RSV or parainfluenza virus is obtained in a subject. This genus reads on a broad array of sequences, probably thousands of sequences, and the disclosure fails to provide a representative number of species for such a broad genus claimed, nor do they adequately describe the elements essential for this genus (e.g. the myriad of sequences within each genus that would successfully target and inhibit the expression of the various target genes claimed). The disclosure does not clarify the common attributes encompassed by this very broad genus and concise structural features that would distinguish structures within the broadly claimed genus of sequences are missing from

the disclosure. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus claimed. Thus, applicant was not in possession of the claimed genus comprising at least 10 or 40 nucleotides in length with anti-viral activity occurring principally by a non-sequence complementary mode of action, and which contain randomer oligonucleotides providing treatment and prophylactic effects claimed.

Claims 1-2, 14-32 and 38 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The first paragraph of 35 U.S.C. 112 states: "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring ingenuity beyond that to be expected of one of ordinary skill in the art (*Fields v. Conover*, 170 USPQ 276 (CCPA 1971) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (*In re Colianni*, 195 USPQ 150 (CCPA 1977).

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those In the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: The claims are drawn to a method for the prevention or treatment of RSV and parainfluenza virus comprising administration of an oligonucleotide at least 10 or 40 nucleotides in length with anti-viral activity occurring principally by a non-sequence complementary mode of action. As such, the claims encompass in vivo therapy treating infected patients by administering one or more oligonucleotides.

The state of the prior art and the predictability or lack thereof in the art: Shiro Shigeta (Expert Opinion on Investigational Drugs, 2000, Vol. 9 No. 2, pages 221-235) teaches the recent progress in antiviral treatment for RSV. Oligodeoxyribonucleotides (ODNs) targeted against RSV genomic RNA were found to inhibit RSV replication in cell culture. Modifications were made to stabilize antisense for digestion by the introduction of phosphothioate ODN but the antisense filed to increase the selectivity of the anti-RSV effect. Because Shigeta teaches that there are still some problems to be solved with antisense ODN including the selection of targeting gene RNA, the stability of the antisense ODN, the delivery of the ODN to the target sense RNA and the sensitivity of

the hybrid to Rnase (page 228), the art teaches that the administration of oligonucleotides for in vivo therapy is highly unpredictable.

The amount of direction or guidance present and the presence or absence of working examples: Enablement must be provided by the specification unless it is well known in the art. *In re Buchner* 18 USPQ 2d 1331 (Fed. Cir. 1991). Because of the high degree of unpredictability taught in the art, the specification must contain sufficient disclosure to enable the claimed invention. There is insufficient disclosure to reasonably predict that the methods and compositions of the instant specification would reduce the susceptibility of RVS or parainfluenza virus infection *in vivo*. This is merely an unsubstantiated assertion with no evidence to support the contention that the *in vitro* studies of the specification are indicative of *in vivo* activity. Applicant has only shown cell culture data, not treating infected patients or shown an art recognized correlation between the data shown and the scope of the claimed invention. The artisan would recognize and appreciate that there is no known correlation between *in vitro* and *in vivo* results, because the artisan recognizes that an *in vitro* assay cannot duplicate the complex conditions of *in vivo* therapy. In the *in vitro* assay, the agent is in contact with cells during the entire exposure period. This is not the case *in vivo* where exposure to the target site may be delayed or inadequate. In addition, variables such as biological stability, half-life, or clearance from the blood are important parameters in achieving successful therapy. The composition may be inactivated *in vivo* before producing a sufficient effect, for example, by proteolytic degradation or immunological activation. In addition, the composition may not reach the target cells because of its inability to

penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells, and tissues where the composition has no effect and/or a large enough local concentration may not be established (see pp. 3-29 in Goodman & Gilman's The Pharmacological Basis of Therapeutics for a discussion of the current state of the art).

The breadth of the claims and the quantity of experimentation needed: Because the art teaches a high degree of unpredictability in predicting the efficacy of therapeutics based solely on in vitro data and because the specification fails to provide sufficient disclosure to overcome the teachings of unpredictability found in the art, it would require undue experimentation by one of skill in the art to be able to practice the claimed invention. There are no specific teachings in the disclosure that would allow one to have a reasonable expectation of success in transferring the *in vitro* method disclosed in applicant's specification to successfully treat infected patients. One is only left with speculation and an invitation to experiment. Therefore, the claimed invention lacks an enabling disclosure.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application

filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-2, 14-15, 17-32 and 38 are rejected under 35 U.S.C. 102(e) as being anticipated by Peyman et al. (US Patent No. 6,013,639).

The claimed invention is drawn to a method for the prophylaxis or treatment of a RSV or parainfluenza virus infection in a subject, preferably a human, comprising administering at least one pharmacologically acceptable oligonucleotide at least 10 or 40 nucleotides in length wherein the anti-viral activity of said oligonucleotide occurs principally by a non-sequence mode of action, wherein the method comprises at least one antiviral randomer oligonucleotide, wherein said oligonucleotide is non complementary to any portion of the genomic sequence of RSV or parainfluenza virus, wherein said formulation has an IC_{50} for RSV or parainfluenza virus of 0.10 μM or less, wherein said oligonucleotide comprises: at least one modification; one phosphorothioated linkage and is in a formulation comprising a delivery system; at least one modification to the ribose moiety; at least one methylphosphonate linkage; at least one phosphorothiolated linkage and is in a formulation comprising a delivery system; wherein said oligonucleotide is a concatemer consisting of two or more oligonucleotide sequences joined by a linker, wherein said oligonucleotide is linked at one or more residues, to a molecule modifying the characteristics of the oligonucleotide to obtain one or more characteristics selected from the group of higher stability, higher antiviral activity, etc., wherein said oligonucleotide is double stranded, binds to one or more viral components, wherein at least a portion of the sequence of said oligonucleotide is

derived from a viral genome, wherein the method comprises a mixture of at least two different antiviral oligonucleotides.

Peyman et al. discloses oligonucleotides where a nucleotide sequence is from 10 to 40 nucleotides in length and can be synthesized chemically. The oligonucleotides are used to treat diseases caused by viruses (Abstract). Stability can be effected by modifying or replacing the phosphate bridge (linkage). The most frequently used are phosphorothioate or methyl phosphonate bridges (Column 1, lines 25-35). Complete or partial replacement of the deoxyribose units, preferably, one, two, or three ribose units should be replaced ((column 4, lines 11-32). The oligonucleotides can be linked to molecules which are known to have a favorable influence on the properties of antisense oligonucleotides (column 4, lines 61-65). Oligonucleotides with chemical modifications demonstrate a higher cell uptake and increased stability (column 1, lines 38-50). The disclosed invention relates to the use of oligonucleotides possessing at least one terminal and modified pyrimidine nucleoside as diagnostic agents for detecting the presence or absence, or the quality, of a specific double-stranded or single-stranded nucleic acid molecule in a biological sample (column 6, lines 15-20).

Peyman teaches sense nucleotides, as well as antisense. While the antisense would be complementary, no part of the sense would be complementary to any part of the viral genome.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Peyman et al. (US Patent No. 6,013,639). The teachings of Peyman et al. have been recited above. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to optimize the formulation with a desired concentration for effective anti-viral activity. The person of ordinary skill in the art would have been motivated to make that modification because an effective amount of a pharmaceutical composition is required for treatment, and reasonably would have expected success because of the data from the *in vitro* experiments.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon Hurt whose telephone number is 571-272-3334. The examiner can normally be reached on M-F 8:00 - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Housel James can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sharon Hurt

April 20, 2006

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